REMARKS

The present communication is intended to supplement applicants' response of September 17, 2001. Certain errors have now been noticed in the drawings, which errors affect the sequence listing. Accordingly, the present amendment is intended to correct the drawings and to correct the sequence listing accordingly. The specification is also being amended to correspond to the corrected sequence identification numbers.

The first correction deals with Figures 1B and 2. It can be seen that in both of these figures as filed the last amino acid of the deduced amino acid sequence was "Z". However, one can see from the nucleotide sequence from which the amino acid sequence was deduced (as can clearly be seen in revised SEQ ID NOs:1 and 3 submitted herewith which show the amino acids of the coding region in the nucleotide sequence) that the nucleotide codon for this amino acid is "taa" in Figure 1A (nucleotides 1922-1924) or "tga" in the nucleotide sequence of Figure 2 (nucleotides 1145-1147). These are stop codons and not "Glx" which is the meaning for amino acid "Z" according to some standard amino acid nomenclatures. Thus the "Glx" as appearing in the original SEQ ID NOs:2 and 4 was clearly in error. In any event, it is clear that the "Z" was used in Figure 1B and Figure 2 to indicate a stop codon. As this is not conventional terminology, it has simply been eliminated from these drawings and from the sequence listing as it is the previous residue which is the last residue which is coded for by the nucleotide sequence.

Accordingly, applicants propose to revise Figures 1B and 2 to delete "Z", the last amino acid residue in line 7 of both figures. The corresponding sequences, i.e., SEQ ID NOs:2 and 4, have been amended accordingly. This is not a new matter as it is merely the correction of an obvious error as discussed above.

Attached hereto are copies of Figures 1B and 2 with the above proposed corrections indicated in red. Please indicate your approval of these proposed changes so that corrected formal drawings can be filed at the appropriate time.

SEQ ID NO:2 has further been amended to add residue "Arg" at position 85. The omission of "Arg" at position 85 was due to a typographical/clerical error. The addition of "Arg" is supported by the corresponding deduced amino acid sequence of Figure 1B which shows "R" at position 85 (fifth residue of second line). It is also very clear from new SEQ ID NO:1 showing the amino acids of the coding region of the nucleotide sequence.

With these corrections to SEQ ID NO:2, it is now seen that it is identical to previous SEQ ID NO:7 and the corrected SEQ ID NO:4 is now identical to previous SEQ ID NO:6. Accordingly, applicants have now deleted all reference to SEQ ID NOs:6 and 7 and have substituted reference to SEQ ID NOs:2 and 4. All of the other SEQ ID numbers after SEQ ID NO:7 have been moved down two numbers. In the revised sequence listing submitted herewith the appropriate amendments to the specification have also been made by the present amendment.

It has also been brought to applicants' attention that Figure 3C contained typographical errors in the sequences of CASP-8 AND CASP-3. Residue 296 of SEQ ID NO:6 (CASP-8) (previously SEQ ID NO:8) should be "Leu" instead of "Trp", residue 331 of SEQ ID NO:6 (CASP-8) should be "Ala" instead of "Gly", and residue 162 of SEQ ID NO:8 (CASP-3) (previously SEQ ID NO:10) should be "Asp" instead of "Glu".

It is evident that these changes do not involve new matter as the sequences in question were identified as known caspase sequences (see page 25, lines 11-29, and page 94, lines 18-24, of the present specification). Attached hereto is the GenBank entry (X98172) for MACH-alpha-1 (now known as CASP-8) and for CASPASE 3 (P42574). Both of these sequences were originally submitted to GenBank well prior to the effective filing date of the present application. The sequences of Figure 3C are now proposed to be corrected so as to correspond to the correct known sequences for these proteins. As these were obvious errors no new matter is involved in correcting them.

Attached hereto is a copy of Figure 3C with the above proposed corrections indicated in red. Please indicate your approval of these proposed changes so that corrected formal drawings can be filed at the appropriate time.

Applicants have made the corrections in the sequences of CASP-8 and CASP-3 in the corresponding SEQ ID NOs:6 and 8. Attached hereto is a substitute paper copy Sequence Listing and a 3 1/2" disk containing the "Sequence

Listing" in computer readable form in accordance with 37 C.F.R. §1.821(e).

The following statement is provided to meet the requirements of 37 C.F.R. §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sheets of the sequence listing are believed to be supported in the application as filed and that the substitute sheets of the sequence listing are not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is the same as the attached substitute paper copy of the sequence listing.

If the examiner has any questions or comments concerning the above described application, the examiner is urged to contact the undersigned at the phone number below.

Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that

organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning at line 11 of page 25 has been amended as follows:

Figure 3 depicts schematically a comparison of the amino acid sequences of the human (hCASHα, hCASHβ) G1 (or CASH) and mouse (mCASHα) splice variants, and conserved motifs found in these proteins. In Figure 3 there is shown a collinear amino acid sequence alignment of mouse G1α (mCASHα) (SEQ ID NO:5), human G1α (hCASHα) (SEQ ID NO:~~7~~2) and G1β (hCASHβ) (SEQ ID NO:~~6~~4), CASP-8 (MACH/FLICE1/Mch5) (SEQ ID NO:~~8~~6), CASP-10 (Mch4/FLICE2) (SEQ ID NO:~~9~~7), CASP-3 (CPP32/Apopain/Yama) (SEQ ID NO:~~10~~8) and CASP-1 (ICE) (SEQ ID NO:~~11~~9). CASP-1 and CASP-3 are shown without their prodomain regions. Amino acid residues are numbered to the right of each sequence. Dotted lines indicate gaps in the sequence to allow optimal alignment. The 'death domain' modules (DED) are shaded. Amino acids that are identical in more than three of the proteins shown are boxed. Within the region of protease homology, amino acids aligned with CASP-1 residues that were implicated in catalytic activity by X-ray crystallography are denoted as follows : The residues putatively involved in catalysis, corresponding to His237 and Cys285 in CASP-1, are darkly shaded and marked by closed circles below the alignment. The residues constituting the binding pocket for the carboxylate side chain of the P1 Asp, corresponding to Arg179, Gln 238, Arg341 and Ser347 in CASP-1, are less heavily

shaded and marked by open circles. Known and suggested Asp-X cleavage sites and the potential site of cleavage found at a similar location in G1 (CASH) are shaded. Horizontal arrows indicate the N- and C- terminal ends of the small and large subunits of the CASP-1. The C-termini of the proteins are denoted by asterisks.

The paragraph beginning at line 21 of page 45 has been amended as follows:

A non-limiting example of how peptide inhibitors of the G1 proteases would be designed and screened is based on previous studies on peptide inhibitors of ICE or ICE-like proteases, the substrate specificity of ICE and strategies for epitope analysis using peptide synthesis. The minimum requirement for efficient cleavage of peptide by ICE was found to involve four amino acids to the left of the cleavage site with a strong preference for aspartic acid in the P_1 position and with methylamine being sufficient to the right of the P_1 position (Sleath et al., 1990; Howard et al., 1991; Thornberry et al., 1992). Furthermore, the fluorogenic substrate peptide (a tetrapeptide), acetyl-Asp-Glu-Val-Asp-a-(4-methyl-coumaryl-7-amide) abbreviated Ac-DEVD-AMC (SEQ ID NO:1~~2~~0), corresponds to a sequence in poly (ADP-ribose) polymerase (PARP) found to be cleaved in cells shortly after FAS-R stimulation, as well as other apoptopic processes (Kaufmann, 1989; Kaufmann et al., 1993; Lazebnik et al., 1994), and is cleaved effectively by CPP32 (a member of the CED3/ICE protease family) and MACH proteases (and likewise also possibly by G1 proteases).

The paragraph beginning at line 13 of page 46 has been amended as follows:

Since it may be advantageous to design peptide inhibitors that selectively inhibit G1 proteases without interfering with physiological cell death processes in which other members of the CED3/ICE family of proteases are involved, the pool of peptides binding to G1 proteases in an assay such as the one described above can be further synthesized as a fluorogenic substrate peptide to test for selective cleavage by G1 proteases without being cleaved by other CED3/ICE proteases. Peptides which are determined to be selectively cleaved by the G1 proteases, can then be modified to enhance cell permeability and inhibit the cell death activity of G1 either reversibly or irreversibly. Thornberry et al. (1994) reported that a tetrapeptide (acyloxy) methyl ketone Ac-Tyr-Val-Ala-Asp-CH_2OC (O)-[2,6-$(CF_3)_2$] Ph (SEQ ID NO:~~13~~1) was a potent inactivator of ICE. Similarly, Milligan et al. (1995) reported that tetrapeptide inhibitors having a chloromethylketone (irreversibly) or aldehyde (reversibly) groups inhibited ICE. In addition, a benzyloxycarboxyl-Asp-CH_2OC (O) -2,6-dichlorobenzene (DCB) was shown to inhibit ICE (Mashima et al., 1995). Accordingly, tetrapeptides that selectively bind to G1 proteases can be modified with, for example, an aldehyde group, chloromethylketone, (acyloxy) methyl ketone or a CH_2OC (O)-DCB group to create a peptide inhibitor of G1 protease activity.

The paragraph beginning at line 7 of page 81 has been amended as follows:

Exploring the nature of this size heterogeneity, cDNA libraries were screened for transcripts that hybridize with the MACHß1 cDNA probe. MACHα1 and MACHα2 were cloned from a Charon BS cDNA library derived from the mRNA of human thymus. The library was screened under stringent conditions with a MACHß1 cDNA probe, labeled using a random-priming kit (Boehringer Mannheim). The other MACH isoforms were cloned by RT-PCR, performed on total RNA from Raji (MACHα1, α2, α3, ß3 and ß4) and Daudi (MACHα2, ß2, ß3, ß4, and β5) human lymphoblastoid cells. Reverse transcriptase reaction was performed with an oligo-dT adapter primer (5'-GACTCGAGTCTAGAGTCGAC$(T)_{17}$-3') (SEQ ID NO:1~~4~~2) and the SuperScript II reverse transcriptase (GIBCO-BRL), used according to the manufacturer's instructions. The first round of PCR was performed with the Expand Long Template PCR System (Boehringer Mannheim) using the following sense and antisense primers: 5'-AAGTGAGCAGATCAGAATTGAG-3' (SEQ ID NO:1~~5~~3), corresponding to nucleotides 530-551 of the MACHß1 cDNA, and 5'-GACTCGAGTCTAGAGTCGAC-3' (SEQ ID NO:1~~6~~4), respectively. The second round was performed with Vent polymerase (NEB) using the following sense and antisense nested primers: 5'GAGGATCCCCAAATGCAAACTGGATGATGAC-3' (SEQ ID NO:1~~7~~5) and 5'-GCCACCAGCTAAAAACATTCTCAA-3' (SEQ ID NO:1~~8~~6), derived from the sequence of MACHß1 cDNA, respectively. To confirm that MACHß3 and MACHß4 have initiation codons, a more 5' sequence

of these isoforms from the RNA of Raji cells was cloned. The RT-PCR reaction, performed using the oligo-dT adapter primer as described above, was followed by two rounds of PCR (with Vent polymerase (NEB)) using the following sense and antisense oligonucleotides: 5'-TTGGATCCAGATGGACTTCAGCAGAAATCTT-3' (SEQ ID NO:1~~9~~7) and 5'-ATTCTCAAACCCTGCATCCAAGTG-3' (SEQ ID NO:~~20~~18), derived from the sequence of MACHß1. The latter oligonucleotide is specific to the ß-isoforms. Among the clones obtained in this way, those found to contain the nucleotides encoding for the amino acids of 'block 2' (whose presence distinguishes MACHß3 and MACHß4 from MACHß1 and MACHß2) were fully sequenced. Nucleotide sequences in all cloned isoforms were determined in both directions by the dideoxy-chain termination method. Only partial cDNA clones of MACHa3 and MACHß2 were obtained. This screening revealed the existence of multiple isoforms of MACH MACH. The amino acid sequences of seven of these isoforms were studied in detail. The results are illustrated diagrammatically and exemplified in the above co-owned co-pending applications, particularly PCT/US96/10521 and IL 117932, where the amino acid sequences of three of the isoforms are compared with known homologs.

The paragraph beginning at line 3 of page 85 has been amended as follows:

To find out if the CED3/ICE homology region in MACHa possesses proteolytic activity, applicants expressed the region that extends from the potential cleavage site upstream to this region, between Asp216 and Ser217, till the C terminus

of the protein in bacteria, as a GST fusion protein. The bacterial lysates were examined for ability to cleave fluorogenic peptide substrates, shown before to be cleaved by other CED3/ICE homologs. Two substrate peptides were used: The first, Acetyl-Asp-Glu-Val-Asp-a-(4-Methyl-Coumaryl-7-Amide) (AC-DEVD-AMC) (SEQ ID NO:10), corresponds to a sequence in poly (ADP-ribose) polymerase (PARP), a nuclear protein found to be cleaved in cells shortly after FAS-R stimulation (Tewari et al., 1995b), as well as in other apoptopic processes (Kaufmann, 1989; Kaufmann et al., 1993; Lazebnik et al., 1994). This fluorogenic substrate is cleaved effectively by CPP32. The second fluorogenic substrate, Acetyl-Tyr-Val-Ala-Asp-AMC (Ac-YVAD-AMC) (SEQ ID NO:11), corresponds to a substrate site for ICE in the IL-1ß precursor. This fluorogenic substrate is cleaved by ICE. Lysates of bacteria expressing the CED3/ICE homology region in MACHα1 cleaved effectively the PARP sequence-derived fluorogenic substrate. They had no measurable proteolytic activity, though, against the IL-1ß-precursor sequence-derived fluorogenic substrate (controls), Ac-YVAD-AMC, which is an ICE cleavage site in IL-1β precursor (Thornberry et al, 1992). The proteolytic activity was blocked by iodacetic acid (5 mM), confirming that it is mediated by a thiol protease. No cleavage was observed with lysates containing the GST-fused MACH CED3/ICE-homology region in which the catalytic cysteine residue Cys_{360} was replaced by Ser. Also, lysates from bacteria that expressed the full-length MACHα1 protein as a

GST-fusion protein did not cleave Ac-DEVD-AMC, probably because of the absence of bacterial enzymes capable of processing the full-length molecule. Nor did cleavage occur with lysates containing either of the two potential cleavage products of the CED3/ICE homology region.

The paragraph beginning at line 27 of page 93 has been amended as follows:

A preliminary sequence of one such G1 isoform, a G1 splice variant, is depicted in Fig. 1A+B, in which ~~the upper sequence~~ Fig. 1A is the nucleotide sequence and ~~the lower sequence~~ Fig. 1B is the deduced amino acid sequence of an ORF starting from ATG (nucleotide No. 482) and terminating at TAA (nucleotide 1921), these start and terminator nucleotides being indicated by asterises (*) in the nucleotide sequence. The G1 splice variant of Fig. 1 has also been putatively designated 'G1α'.

The paragraph beginning at line 14 of page 95 has been amended as follows:

Based on the nucleotide sequence of an EST clone found to correspond to the mouse homologue of part of the 'death domain' (DED) region in G1, the cDNAs of both the mouse CASHα and CASHβ splice variants were cloned from mouse liver mRNA by RT-PCR. An EST clone (GenBank accession no. AA198928) was identified as the mouse homologue of part of the DED region in G1. Based on this sequence the mouse G1α (CASHα)

and G1β (CASHβ) splice variants from mouse liver mRNA were cloned by RT-PCR. The reverse transcriptase reaction was performed with an oligo-dT adapter primer (5'-GACTCGAGTCTAGAGTCGAC$(T)_{17}$-3') (SEQ ID NO:~~14~~12) and the AMV reverse transcriptase (Promega), used according to the manufacturer's instructions. The first round of PCR was carried out with the Expand Long Template PCR System (Boehringer Mannheim) using the following sense and antisense primers : 5'-GGCTTCTCGTGGTTCCCAGAGC-3' (SEQ ID NO:~~21~~19), and 5'-GACTCGAGTCTAGAGTCGAC-3' (base pairs 1-20 of SEQ ID NO:1~~4~~2) (adapter) respectively. The second round was performed with Vent polymerase (NEB) using the nested sense primer : 5'-TGCTCTTCCTGTGTAGAGATG-3' (SEQ ID NO:2~~2~~0), and adapter.

1:X98172 . H.sapiens mRNA for...[gi:1403318] PubMed, Protein, Related Sequences, LinkOut

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  TITLE     Involvement of MACH, a novel MORT1/FADD-interacting protease, in
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  JOURNAL   Cell 85 (6), 803-815 (1996)
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  JOURNAL   Submitted (24-MAY-1996) D. Wallach, The Weizmann Institute, Dept of
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            Membrane Research & Biophysics, Rehovot 76100, ISRAEL
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  TITLE     A CASP-8 mutation recognized by cytolytic T lymphocytes on a human
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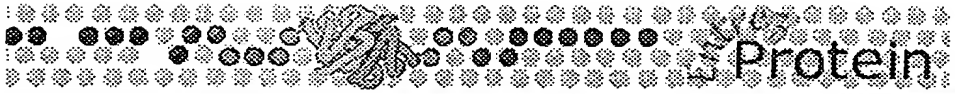

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            InterPro IPR002398, Pfam PF00655, Pfam PF00656, PRINTS PR00376,
            PROSITE PS01122, PROSITE PS01121, PROSITE PS50207, PROSITE PS50208
KEYWORDS    Hydrolase; Thiol protease; Zymogen; Apoptosis; Polymorphism;
            3D-structure.
SOURCE      human.
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 277)
  AUTHORS   Fernandes-Alnemri,T., Litwack,G. and Alnemri,E.S.
  TITLE     CPP32, a novel human apoptotic protein with homology to
            Caenorhabditis elegans cell death protein Ced-3 and mammalian
            interleukin-1 beta-converting enzyme
  JOURNAL   J. Biol. Chem. 269 (49), 30761-30764 (1994)
  MEDLINE   95074098
  REMARK    SEQUENCE FROM N.A. (ALPHA AND BETA ISOFORMS).
            TISSUE=T-cell
REFERENCE   2  (residues 1 to 277)
  AUTHORS   Tewari,M., Quan,L.T., O'Rourke,K., Desnoyers,S., Zeng,Z.,
            Beidler,D.R., Poirier,G.G., Salvesen,G.S. and Dixit,V.M.
  TITLE     Yama/CPP32 beta, a mammalian homolog of CED-3, is a
            CrmA-inhibitable protease that cleaves the death substrate
            poly(ADP-ribose) polymerase
  JOURNAL   Cell 81 (5), 801-809 (1995)
  MEDLINE   95292347
  REMARK    SEQUENCE FROM N.A.
REFERENCE   3  (residues 1 to 277)
  AUTHORS   Nicholson,D.W., Ali,A., Thornberry,N.A., Vaillancourt,J.P.,
            Ding,C.K., Gallant,M., Gareau,Y., Griffin,P.R., Labelle,M.,
            Lazebnik,Y.A., Munday,N.A., Raju,S.M., Smulson,M.E., Yamin,T.-T.,
            Li,V.L. and Miller,D.K.
  TITLE     Identification and inhibition of the ICE/CED-3 protease necessary
            for mammalian apoptosis
  JOURNAL   Nature 376 (6535), 37-43 (1995)
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MEDLINE 95319529
REMARK SEQUENCE OF 29-46 AND 175-193, AND FUNCTION.
REFERENCE 4 (residues 1 to 277)
AUTHORS Rotonda,J., Nicholson,D.W., Fazil,K.M., Gallant,M., Gareau,Y., Labelle,M., Peterson,E.P., Rasper,D.M., Ruel,R., Vaillancourt,J.P., Thornberry,N.A. and Becker,J.W.
TITLE The three-dimensional structure of apopain/CPP32, a key mediator of apoptosis
JOURNAL Nat. Struct. Biol. 3 (7), 619-625 (1996)
MEDLINE 96266352
REMARK X-RAY CRYSTALLOGRAPHY (2.5 ANGSTROMS) OF 28-277.
REFERENCE 5 (residues 1 to 277)
AUTHORS Mittl,P.R., Di Marco,S., Krebs,J.F., Bai,X., Karanewsky,D.S., Priestle,J.P., Tomaselli,K.J. and Grutter,M.G.
TITLE Structure of recombinant human CPP32 in complex with the tetrapeptide acetyl-Asp-Val-Ala-Asp fluoromethyl ketone
JOURNAL J. Biol. Chem. 272 (10), 6539-6547 (1997)
MEDLINE 97197830
REMARK X-RAY CRYSTALLOGRAPHY (2.3 ANGSTROMS) OF 35-173 AND 185-277.
REFERENCE 6 (residues 1 to 277)
AUTHORS Lee,D., Long,S.A., Adams,J.L., Chan,G., Vaidya,K.S., Francis,T.A., Kikly,K., Winkler,J.D., Sung,C.-M., Debouck,C., Richardson,S., Levy,M.A., DeWolf,W.E.Jr, Keller,P.M., Tomaszek,T., Head,M.S., Ryan,M.D., Haltiwanger,R.C., Liang,P.-H., Janson,C.A., McDevitt,P.J., Johanson,K., Concha,N.O., Chan,W., Abdel-Meguid,S.S., Badger,A.M., Lark,M.W., Nadeau,D.P., Suva,L.J., Gowen,M. and Nuttall,M.E.
TITLE Potent and selective nonpeptide inhibitors of caspases 3 and 7 inhibit apoptosis and maintain cell functionality
JOURNAL J. Biol. Chem. 275 (21), 16007-16014 (2000)
MEDLINE 20283632
REMARK X-RAY CRYSTALLOGRAPHY (2.8 ANGSTROMS).
REFERENCE 7 (residues 1 to 277)
AUTHORS Fernandes-Alnemri,T., Armstrong,R.C., Krebs,J., Srinivasula,S.M., Wang,L., Bullrich,F., Fritz,L.C., Trapani,J.A., Tomaselli,K.J., Litwack,G. and Alnemri,E.S.
TITLE In vitro activation of CPP32 and Mch3 by Mch4, a novel human apoptotic cysteine protease containing two FADD-like domains
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 93 (15), 7464-7469 (1996)
MEDLINE 96353838
REMARK PROCESSING.
REFERENCE 8 (residues 1 to 277)
AUTHORS Goldberg,Y.P., Nicholson,D.W., Rasper,D.M., Kalchman,M.A., Koide,H.B., Graham,R.K., Bromm,M., Kazemi-Esfarjani,P., Thornberry,N.A., Vaillancourt,J.P. and Hayden,M.R.
TITLE Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract
JOURNAL Nat. Genet. 13 (4), 442-449 (1996)
MEDLINE 96331285
REMARK CLEAVAGE OF HUNTINGTIN.
COMMENT ----------

[FUNCTION] INVOLVED IN THE ACTIVATION CASCADE OF CASPASES RESPONSIBLE FOR APOPTOSIS EXECUTION. AT THE ONSET OF APOPTOSIS IT PROTEOLYTICALLY CLEAVES POLY(ADP-RIBOSE) POLYMERASE (PARP) AT A 216-ASP-|-GLY-217 BOND. CLEAVES AND ACTIVATES STEROL REGULATORY ELEMENT BINDING PROTEINS (SREBPS) BETWEEN THE BASIC HELIX-LOOP-HELIX LEUCINE ZIPPER DOMAIN AND THE MEMBRANE ATTACHMENT DOMAIN. CLEAVES AND ACTIVATES CASPASE-6, -7 AND -9. INVOLVED IN THE CLEAVAGE OF HUNTINGTIN.

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            [ENZYME REGULATION] INHIBITED BY ISATIN SULFONAMIDES.
            [SUBUNIT] HETERODIMER OF A 17 KDA (P17) AND A 12 KDA (P12) SUBUNIT.
            [SUBCELLULAR LOCATION] CYTOPLASMIC.
            [TISSUE SPECIFICITY] HIGHLY EXPRESSED IN LUNG, SPLEEN, HEART, LIVER
            AND KIDNEY. MODERATE LEVELS IN BRAIN AND SKELETAL MUSCLE, AND LOW
            IN TESTIS. ALSO FOUND IN MANY CELL LINES, HIGHEST EXPRESSION IN
            CELLS OF THE IMMUNE SYSTEM.
            [PTM] CLEAVAGE BY GRANZYME B, APAF-1, CASPASE-6, -8 AND -10
            GENERATES THE TWO ACTIVE SUBUNITS. ADDITIONAL PROCESSING OF THE
            PROPEPTIDES IS LIKELY DUE TO THE AUTOCATALYTIC ACTIVITY OF THE
            ACTIVATED PROTEASE. ACTIVE HETERODIMERS BETWEEN THE SMALL SUBUNIT
            OF CASPASE-7 PROTEASE AND THE LARGE SUBUNIT OF CPP32 ALSO OCCUR AND
            VICE VERSA.
            [SIMILARITY] BELONGS TO PEPTIDASE FAMILY C14; ALSO KNOWN AS THE
            CASPASE FAMILY.
FEATURES             Location/Qualifiers
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                     1..277
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     Protein         1..277
                     /product="APOPAIN PRECURSOR"
                     /EC_number="3.4.22.-"
     Region          10..28
                     /region_name="Propeptide"
     Region          29..175
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                     /note="APOPAIN P17 SUBUNIT."
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                     /note="BY SIMILARITY."
     Site            163
                     /site_type="active"
                     /note="BY SIMILARITY."
     Region          176..277
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                     /note="APOPAIN P12 SUBUNIT."
     Region          190
                     /region_name="Variant"
                     /note="D -> E (IN ISOFORM BETA). /FTId=VAR_001401."
ORIGIN
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       61 mtsrsgtdvd aanlretfrn lkyevrnknd ltreeivelm rdvskedhsk rssfvcvlls
      121 hgeegiifgt ngpvdlkkit nffrgdrcrs ltgkpklfii qacrgteldc gietdsgvdd
      181 dmachkipvd adflyaysta pgyyswrnsk dgswfiqslc amlkqyadkl efmhiltrvn
      241 rkvatefesf sfdatfhakk qipcivsmlt kelyfyh
//
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